Cognitive Dysfunction in Patients with Systemic Lupus Erythematosus: A Controlled Study

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ABSTRACT. ***Objective.*** To determine the extent to which cognitive dysfunction (CD) observed in patients with systemic lupus erythematosus (SLE) exceeds that seen in a matched control group of patients with rheumatoid arthritis (RA), and to estimate the prevalence of CD in SLE in a community-based sample.

Methods. A random subsample of 31 patients with SLE was compared to patients with RA matched by age, sex, and race and derived from the same patient population. Cognitive function was assessed by the Automated Neuropsychological Assessment Metrics (ANAM). The primary outcome was the total throughput score (number of correct responses divided by the time taken for those responses averaged over all subtests), adjusted for premorbid intelligence, neuromuscular efficiency, disease activity, damage, depression, fatigue, and health-related quality of life.

Results. There were no statistically significant differences in mean throughput scores between patients in the SLE and RA groups in any subtest of the ANAM or in the total throughput score. The frequency of CD, defined as either total scores > 1.5 SD below the mean of the RA population, or 4 or more ANAM subtests each > 1.5 SD below the RA mean, was similar in patients with SLE and in RA controls.

Conclusion. We found no differences in cognitive function between patients with SLE and RA, suggesting that the CD found in some patients with SLE may represent the consequences of a chronic and/or inflammatory disease rather than SLE-related central nervous system damage. (J Rheumatol First Release April 1 2011; doi:10.3899/jrheum.100560)

Key Indexing Terms:

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RHEUMATOID ARTHRITIS
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Cognitive dysfunction (CD) is one of the most common manifestations of neuropsychiatric systemic lupus erythematosus (NPSLE). It has been reported to occur in 12% to 87% of patients with SLE[1,2,3]. These divergent prevalence estimates likely reflect the difficulties involved in studying this manifestation of SLE as well as the differences in populations studied, methods of assessment, and definitions of CD.

With rare exceptions, previous studies have evaluated patients from tertiary referral centers[2,3,4,5,6]. Patients seen in academic medical centers may not be representative of the larger population of patients with SLE[7]. As recommended by the Ad Hoc Committee of the American College of Rheumatology (ACR), most studies of CD in patients with SLE have used traditional neuropsychologic tests[8]. However, it remains unclear which tests should be used and how CD should be defined based on the scores of the individual standardized tests used for cognitive assessment. This has given rise to variable implementation of tests and interpretation of their results. Recently, a computerized battery of tests designed to measure cognitive function, the Automated Neuropsychological Assessment Metrics (ANAM), has been used to assess patients with SLE, with encouraging results[5,6,9,10,11,12].

CD has been defined in most studies relative to normal controls. But many chronic diseases may cause pain, depression, fatigue, and anxiety. Any of these may affect cognitive performance[13,14,15]. Other, unmeasured effects of chronic inflammatory diseases may also affect cognitive function. Only a few studies have recognized the potential confounding effects of chronic disease[1,12,15,16,17]. Using rheumatoid arthritis (RA) and multiple sclerosis controls, recent work by Hanly, *et al* suggests that there may be no significant dif-

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ferences in cognitive function between patients with SLE and those with RA, as measured either by mean cognitive function scores or by frequency of CD[12]. With rare exceptions, previous studies have not taken premorbid intelligence into consideration[4]. Failure to adjust for premorbid intelligence could result in misclassification with both false-positive (patients with low premorbid intelligence who score low) and false-negative determinations (patients with high premorbid intelligence who now fall within the "normal" range).

We performed a case-control study of a community-based cohort of patients with SLE using a similarly derived RA control population matched by age, sex, and race to assess cognitive function, with adjustment for disease severity and premorbid intelligence. Our intention was to determine the extent to which the CD observed in patients with SLE was more frequent or more severe than that found in RA.

MATERIALS AND METHODS

Patients. A random subsample of patients with SLE referred by community-based primary care physicians was examined. Community-based patients were those who had been referred by primary care physicians not affiliated with an academic medical center or a hospital-based clinic to a group of 4 rheumatologists. These patients may or may not have been hospitalized previously for SLE. All patients from this referral source meeting the updated ACR classification criteria were identified and enumerated[18]. A random number table was used to identify a total of 90 patients. It was assumed that the participation rate would be about 50% and that 45 patients were needed to have reasonable power. Of the 90 patients, 44 (48.9%) agreed to participate. Of these, we were able to match, schedule, and evaluate 31 subjects with SLE. Patients were excluded if they had had a history of head injury that led to unconsciousness, were < 18 years of age, or had unstable disease necessitating an increase in prednisone dose or the addition of another immunosuppressive medication. Controls consisted of patients being followed in the same practice who met the 1987 ACR classification criteria for RA[19]. Patients with SLE and controls were matched for age (± 5 years), sex, and race.

The research was approved by the University of Cincinnati Institutional Review Board, and all patients signed an informed consent after careful discussion of the risks and benefits of participation.

Study design. Participants were evaluated cross-sectionally, typically at a time that coincided with their routine office visit. Evaluations lasted about 2 hours. Baseline demographic information was obtained as well as information on income, education, occupation, smoking history, medical history, and concomitant medication use.

Disease characteristics. SLE disease activity was assessed using the SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index)[20]. Damage was assessed using the SLICC (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SDI)[21]. RA disease activity was evaluated using the 28-joint count Disease Activity Score (DAS28)[22], and functional status in patients with RA was assessed by the Health Assessment Questionnaire (HAQ)[23]. Fatigue and depression were assessed in both groups using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT)[24] and the Beck Depression Inventory II[25], respectively. Further, patients completed visual analog scales of pain, subjective disease activity, and global assessment of health status. The Medical Outcomes Survey Short-Form 36 (SF-36, v2) was also completed by each subject as a measure of health-related quality of life[26].

Premorbid intelligence was estimated by the Peabody Picture Vocabulary Test Revised (PPVT-R), a reasonably reliable indicator of premorbid intelligence in patients with mild to moderate CD[27,28]. It measures receptive vocabulary, which may be less affected by mild CD than reading vocabulary, upon which other, similar tests are based[29].

Assessment of cognitive function — ANAM. Cognitive function was evaluated using the ANAM. The ANAM is a self-administered, computer-based battery of neurocognitive tests that was developed to test some of the same cognitive domains as probed by formal neuropsychological testing but more efficiently, and without the need for trained personnel for administration[30,31]. The ANAM4 consists of 8 subtests and simple reaction time (SRT), which measures neuromuscular response efficiency. Other subtests measure learning and recall, both short-term and longer term, working memory, sustained attention, logical reasoning, and visual-spatial processing. The ANAM has been validated as a reliable measure of cognitive function in patients with traumatic brain injury, multiple sclerosis, and early Alzheimer's disease[32,33,34,35]. Several studies have used the ANAM to evaluate cognitive function in patients with SLE, both adults and children; the ANAM was found to be an accurate measure of cognitive function that correlated well with formal neuropsychological testing[5,6,9]. Roebuck-Spencer, *et al* found that the ANAM has a sensitivity of 76.2%, a specificity of 82.8%, and an accuracy of 80% for diagnosing CD in SLE[5]. Similarly, using a modified version of the ANAM for the pediatric age group, Brunner, *et al* demonstrated that individual ANAM measurements had an area under the receiver operating curves (AUC) of 0.75 to 0.83, and when combinations of measurements were used, the AUC increased further to 0.96, for correctly identifying patients with SLE who had CD[6].

Primary outcome measures. The primary outcome measure chosen for our study was the mean total throughput score (TTS). This measurement has been used in other studies using the ANAM in adult patients with SLE. Throughput is defined as the number of correct responses divided by the time required for the correct responses for each of the subtests. The TTS is the total of the throughput scores for each of the 8 subtests of the ANAM. Because of the possible influence of neuromuscular dysfunction or pain on time to respond, all scores were adjusted for SRT. Responses on the ANAM require repetitive manipulation of the computer mouse. Musculoskeletal or neurologic problems could decrease throughput scores as a direct result of decreased physical function, independent of cognitive function. The SRT is the time to react to the appearance of a blinking symbol on the computer screen. It is a preliminary routine of the ANAM that appears to measure neuromuscular reaction time exclusively. Adjusted inverse efficiency (AIE) has been suggested as an alternative means to control for this phenomenon[12,36]. AIE equals the average time required to obtain the correct responses minus the average time of SRT, divided by the percentage of correct responses. AIE were also computed for each patient and for each subtest.

Definition of CD. For our study, CD was defined in 2 ways: CD1 represents TTS lower than 1.5 SD below the mean of the matched RA population; and CD2, by analogy with traditional neuropsychological testing, scores lower than 1.5 SD below the mean of the patients with RA in ≥ 4 of the 8 ANAM subtests. The throughput scores were about normally distributed. Accordingly, 93% of patients with RA would be expected to have scores greater than or equal to this value.

Statistics. Descriptive statistics and their distributions were computed. Bivariate analyses were undertaken using Wilcoxon rank sum test or T tests, depending on the distribution of the variable under consideration. Fisher's exact test was used for comparing the frequencies of categorical variables between groups. Multiple linear regression was used to identify independent predictors of TTS and to test for group differences in the TTS while adjusting for potential confounders. Logistic regression was used to identify predictors and to assess the influence of the diagnosis of SLE on the development of CD in this context.

RESULTS

Patients. Ninety patients with SLE were randomly selected from a community-based population and 44 agreed to participate in the study. We were able to match 31 patients with

SLE to 31 RA controls. The only significant difference between the groups in demographic characteristics was in income distribution; compared to patients with SLE, those with RA were more likely to have family incomes > US$100,000 (Table 1). Estimates of premorbid intelligence (mean ± SD) were similar in both groups (PPVT-R: SLE vs RA = 103.0 ± 11.2 vs 101.6 ± 10.9, respectively).

Patients with SLE had mild to moderate disease activity (mean ± SD SLEDAI-2K = 5.6 ± 4.7), had moderate amount of damage (mean ± SD SDI = 1.9 ± 1.9), and were clinically stable at the time of assessment. This was also true for most patients with RA, who had a mean DAS28 score of 2.87 and a mean HAQ score of 0.86. However, patients with SLE differed significantly from those with RA in their overall global assessment, prednisone use, depression, and SF-36-MCS (mental component summary; Table 2).

Differences in cognitive performance between RA and SLE. Table 3 presents the throughput scores for each of the subtests together with the TTS. In bivariate analyses, individual throughput scores and TTS of patients with SLE did not differ significantly from those of patients with RA.

When adjusted for SRT and other potential confounders that were found to be different between study groups (family income, patient global assessment, depression, prednisone use, and SF-36-MCS), the TTS scores in SLE and RA were again found to be comparable (SLE 291.65 ± 12.1, RA 289.64 ± 11.9; p = 0.89). The diagnosis of SLE did not affect TTS (standardized coefficient = 0.06, t = 0.40, p = 0.69) in the model. When total adjusted inverse efficiency (AIE) scores were analyzed, there were again no significant differences in any of these individual scores, nor in the aggregate score, between patients with SLE and RA, as shown in Table 4. The presence of SLE did not influence AIE scores (standardized coefficient for presence vs absence of SLE = –0.02, t = –0.14, p = 0.89) and the mean total AIE scores adjusted for the other covariates were similar (SLE: 153.15 ± 8.7 vs RA: 148.80 ± 8.8; p = 0.73).

Frequency of CD. Using the first definition of CD (CD1),

Table 1. Demographics of study population. Except where stated otherwise, the numbers are percentages.

Characteristic	SLE, n = 31	RA, n = 31	p
Age, yrs, mean ± SD	46.1 ± 11.6	47.0 ± 11.3	NS
Women	100	100	NS
Ethnicity			NS
White	71.0	73.3	
African American	22.6	23.3	
Hispanic	3.2	3.2	
Education			NS
Master's degree	16.1	9.7	
Bachelor's degree	29	41.9	
Some college	25.8	25.8	
High school	29	22.6	
Marital status			NS
Married	64.5	60.0	
Divorced	22.6	16.7	
Widowed	0	6.7	
Single	12.9	16.7	
Family income, US $			0.020
> 100K	6.5	36.7	
50K–100K	51.6	30	
20K–49K	35.5	23.3	
< 20K	6.5	6.5	
PPVTS, mean ± SD	102.5 ± 11.5	101.4 ± 11.0	NS

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; PPVTS: Peabody Picture Vocabulary Tests Standardized Revised — estimate of premorbid intelligence; NS: not significant.

Table 2. Disease and treatment characteristics. Except where indicated otherwise, all values are mean ± SD.

Characteristic	SLE	RA	p
Disease duration, yrs	11.5 ± 6.5	9.6 ± 8.0	0.06
SLEDAI-2K	5.5 ± 4.6	NAp*	—
SLICC	1.9 ± 1.9	NAp*	—
HAQ	NAp**	0.89 ± 0.9	—
DAS28	NAp**	2.89 ± 1.59	—
PGA	41.5 ± 18.6	53.1 ± 22.8	0.022
Pain, 0–100 mm	35.3 ± 20.8	28.2 ± 26.0	NS
BDI	18.0 ± 10.4***	9.1 ± 5.4	0.0002
FACIT	26.9 ± 11.9	20.3 ± 9.9	0.056
SF-36-MCS	42.3 ± 12.7	48.8 ± 8.6	0.027
SF-36-PCS	35.2 ± 9.7	41.2 ± 12.2	0.061
Prednisone use, %	45.2	13.3	0.015
Antidepressant use, %	16.1	9.7	0.11
Hydroxychloroquine use, %	41.9	30.0	NS
Opioid use, %	17.9	20.0	NS
ASA use, %	6.7	10.7	NS

*SLE-specific measure. **RA-specific measure. *** 13/31 (42%) patients with SLE were moderately to severely depressed vs 2/32 (6%) RA patients (p < 0.001). SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; HAQ: Health Assessment Questionnaire; DAS28: 28-joint count Disease Activity Score; PGA: physician's global assessment; BDI: Beck Depression Inventory; FACIT: Functional Assessment of Chronic Illness Therapy Fatigue scale; SF-36-MCS: Medical Outcomes Study Short-Form-36 mental component summary; SF-36-PCS: SF-36 physical component summary; ASA: acetylsalicylic acid; NS: not significant.

Table 3. Automated Neuropsychological Assessment Metrics (ANAM) mean throughput scores. All results reported as mean ± SD.

ANAM Subtest	SLE	RA	p
Code substitution learning	36.4 ± 9.6	37.1 ± 8.8	NS
Code substitution delay	31.5 ± 14.4	26.3 ± 11.2	NS
Logical relations	20.1 ± 9.2	20.1 ± 6.4	NS
Matching grids	25.1 ± 7.2	24.6 ± 7.3	NS
Matching to sample	22.5 ± 7.6	25.2 ± 9.1	NS
Mathematical processing	18.1 ± 7.1	20.5 ± 5.2	NS
Sternberg memory search	68.4 ± 24.3	69.4 ± 15.7	NS
Continuous performance task	62.8 ± 34.9	66.1 ± 28.8	NS
Simple reaction time	186.6 ± 50.1	183.5 ± 40.0	NS
Total throughput	285.0 ± 93.1	289.3 ± 65.0	NS

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; NS: not significant.

Table 4. Adjusted inverse efficiency (AIE) scores. All results reported as mean ± SD.

ANAM Subtest	SLE	RA	p
Code substitution learning	13.6 ± 4.1	13.7 ± 3.9	NS
Code substitution delay	17.1 ± 8.2	19.5 ± 8.8	NS
Logical relations	31.4 ± 16.5	28.9 ± 9.9	NS
Matching grids	21.1 ± 6.3	22.1 ± 6.7	NS
Matching to sample	25.1 ± 9.6	23.3 ± 11.4	NS
Mathematical processing	34.6 ± 17.4	28.2 ± 10.9	NS
Sternberg memory search	7.1 ± 8.9	5.6 ± 2.7	NS
Continuous performance task	6.7 ± 12.8	5.9 ± 8.2	NS
Total AIE	156.7 ± 55.8	147.2 ± 40.6	NS

ANAM: Automated Neuropsychological Assessment Metrics; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; NS: not significant.

which considers all subjects with a TTS < –1.5 SD below the mean of the RA control group as abnormal, 19.4% (95% CI 5%, 33%) of patients with SLE were classified as having CD, while 3.2% (95% CI 0.0%, 9.4%) of patients with RA were so classified (SLE vs RA, p = 0.10). However, the presence of CD1 was significantly affected by SRT scores and family income, which were not balanced between the groups. After adjustment for these covariates, 9.7% (95% CI 0%, 20%) of patients with SLE had CD1 while 6.5% (95% CI 0%, 15.1%) of those with RA had CD so defined (p = 0.61). Using total AIE scores in an analogous manner, CD1 was also found in 9.7% of patients with SLE and in 6.5% of patients with RA (Figure 1).

Using the second definition (CD2: ≥ 4/8 subtests of the ANAM, each with scores < –1.5 SD below the RA mean), 3.2% of patients with SLE were considered to have CD2 and 3.2% of patients with RA also had CD2 (Figure 1). When AIE scores were used to determine CD by this second definition, identical results were obtained: 3.2% of both groups had CD2. Logistic regression models using either definition of CD2 yielded similar results. The diagnosis of SLE did not significantly increase the OR in either model (CD2-TTS OR 0.66, 95% CI 0.34, 12.8, p = 0.78; CD2-AIE OR 0.77, 95% CI 0.4%, 13.9%, p = 0.86).

DISCUSSION

In a community-based sample of patients with SLE, cognitive function as measured by the ANAM was not significantly different from that of a matched control group of patients with RA. These results confirm a report by Hanly, *et al*[12], who also used the ANAM and found no differences in the level of cognition between patients with SLE and those with RA as measured by both throughput and AIE scores. They also reported that the frequency of CD, defined in the same way as our CD2 definition, was not significantly different between patients with SLE and those with RA (11% vs 9%, respectively). The type of their study population is not completely clear but appears to have been population-based. Like our study, adjustments were made for age, fatigue, education, and neuromuscular efficiency. They also measured fatigue during testing directly, which we have not done. However, unlike our study, they did not adjust for premorbid intelligence, although education is a reasonable

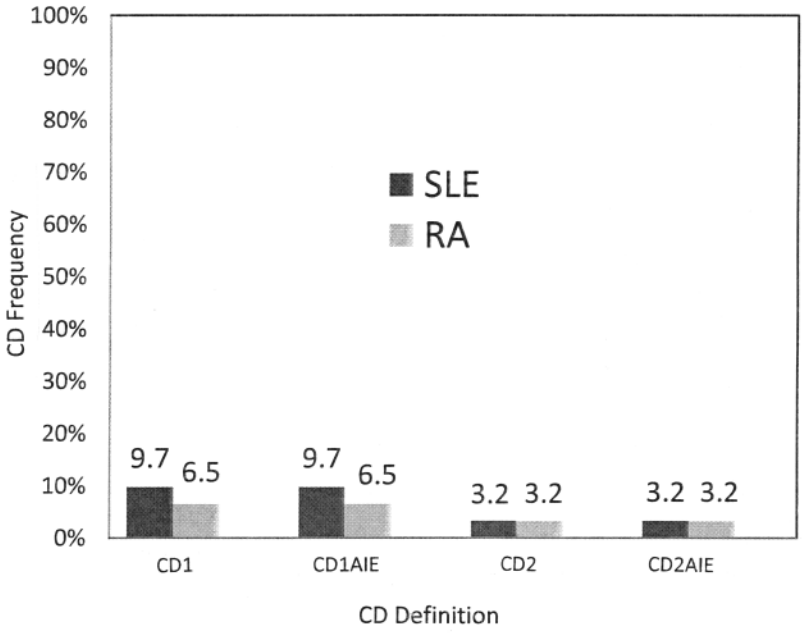

Figure 1. Frequency of cognitive dysfunction (CD) in systemic lupus erythematosus (SLE) compared to rheumatoid arthritis (RA) by various definitions. CD1: cognitive dysfunction (CD) by definition 1 (total throughput score < 1.5 SD of RA mean); CD1AIE: CD by adjusted inverse efficiency (AIE) and definition 1; CD2: CD by definition 2 (≥ 4/8 subtests below 1.5 SD of RA mean); CD2AIE: CD by AIE and definition 2.

surrogate. And, unlike our study, no adjustments were made for disease severity across diagnostic groups. Nonetheless, the use of similar techniques in similar populations has resulted in consistent results.

It is difficult to reconcile our study with those of others who have used very different methods. Even among those studies using the ANAM, differences in results have been reported. In part this may be because some investigators have studied referral populations, some have not used chronic disease controls, and others have not controlled for differences in important covariates such as depression, pain, fatigue, or disease severity. And even if all other things were equal, the operational definitions of CD that were chosen have differed considerably, making direct comparisons difficult.

Using a community-based population, we have found the frequency of CD in SLE to be lower than previously reported and comparable to that found in another chronic, painful, inflammatory rheumatic disease. Patients with RA, however, may not have normal cognition, as suggested by Appenzeller, *et al*[37] and Hanly, *et al*[38]. It is unclear whether the impairment in RA is related to inflammatory processes or premature cerebrovascular disease, or whether it represents the nonspecific effects of a chronic, painful, and potentially debilitating disorder. Although our RA sample was small, we did not find a correlation between cognitive function and any measure of disease activity or severity, suggesting that it may be a nonspecific effect. Nonetheless, until an appropriately controlled study of sufficient size is performed, it will not be possible to distinguish between these possibilities. Regardless of the mechanism, the fact that patients with SLE did not appear to have more frequent (or more severe) CD supports the notion that supportive care and treatment of depression, fatigue, pain, sleep disturbances, and so forth might be the more appropriate initial therapeutic approach. At the same time, there are clearly patients with SLE who have CD that compromises their ability to function and impairs their quality of life. The use of chronic disease controls to define CD may permit the more reliable identification of patients who require a different diagnostic and therapeutic approach.

One of the strengths of our study is our community-based study population, which may be more representative of the general population of patients with SLE. Another is the comprehensive attempt to take into account most of the important covariates that could influence cognitive function, including premorbid intelligence. Finally, we matched our patients with patients with RA for age, sex, race, and treating physician (when possible). Since age is one of the most important predictors of cognitive function, at least as measured by the ANAM, it is important that it be precisely accounted for in the analysis. With the smaller study samples examined in most studies to date, including our own, matching for age as we have done may be a more efficient way of controlling for its effect than adjustment.

Our study has several limitations, the most important of which is the small sample size. This can clearly give rise to a type II error, with failure to detect a difference when one truly exists. However, power calculations suggest that we had an 80% chance of detecting a 20% difference in TTS. We do not mean to suggest that there are no differences in cognitive function between patients with SLE and those with RA, only that the frequency of significant CD in patients with SLE is considerably lower than previously reported. The failure to detect a difference in a study of this power is consistent with that assertion.

Another potential limitation concerns the likelihood that only stable patients who were feeling well chose to participate. We did require disease stability as one of our eligibility criteria, but it turned out that we did not need to exclude any patients on this basis. Nonetheless, it still seems likely that those patients who were not feeling well may not have elected to participate. We did contact most patients on 2 or 3 occasions over a period of time and offered them the opportunity to join the research. This approach should have recruited most patients who were interested in participating but were unable to do so because of a transient flare of their disease. But patients with more persistent activity or more severe disease may still not have participated. We do not know the exact numbers of such patients as we do not have reliable information on activity and severity of the nonparticipants. We would suspect that the numbers were small given the type of study population. Our random selection method should tend to minimize this bias or at least permit us to more precisely determine the denominator of all who were asked to participate. Our participation rate of 48.9% was comparable to that reported by Wendler, *et al* in their review of 10 large intervention trials (41.8% in non-Hispanic whites)[39] and by Sykes, *et al,* who found a participation rate of 22%–69% in whites in survey research[40]. Participation rate is generally not available in observational studies of SLE, which are often based on convenience samples. And this bias is more likely to be a threat to validity in those study samples derived from populations with more severe disease, where participation rates are likely to be even lower.

Because of the rigor of our methods and the similarity of our results to those recently reported, our conclusions are valid and have important implications for the evaluation and treatment of patients with SLE suspected of having CD.

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REFERENCES

1. Hanly JG, Fisk JD, Sherwood G, Jones E, Jones JV, Eastwood B. Cognitive impairment in patients with systemic lupus erythematosus. J Rheumatol 1992;19:562-7.
2. Brey RL, Holliday SL, Saklad AR, Navarrete MG,

Hermosillo-Romo D, Stallworth CL, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 2002;58:1214-20.
3. Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 2001;57:496-500.
4. Lapteva L, Nowak M, Yarboro CH, Takada K, Roebuck-Spencer T, Weickert T, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. Arthritis Rheum 2006;54:2505-14.
5. Roebuck-Spencer TM, Yarboro C, Nowak M, Takada K, Jacobs G, Lapteva L, et al. Use of computerized assessment of predict neuropsychological functioning and emotional distress in patients with systemic lupus erythematosus. Arthritis Rheum 2006; 55:434-41.
6. Brunner HI, Ruth NM, German A, Nelson S, Passo MH, Roebuck-Spencer T, et al. Initial validation of the Pediatric Automated Neuropsychological Assessment Metrics for childhood-onset systemic lupus erythematosus. Arthritis Rheum 2007;57:1174-82.
7. Ward MM. Severity of illness in patients with systemic lupus erythematosus hospitalized at academic medical centers. J Rheumatol 2005;32:27-33.
8. American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599-608.
9. Holliday SL, Navarrete MG, Hermosillo-Romo D, Valdez CR, Saklad AR, Escalante A, et al. Validating a computerized neuropsychological test battery for mixed ethnic lupus patients. Lupus 2003;12:697-703.
10. McLaurin EY, Holliday SL, Williams P, Brey RL. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. Neurology 2005;25:297-303.
11. Petri M, Naqibuddin M, Carson KA, Sampedro M, Wallace DJ, Weisman MH, et al. Cognitive function in a systemic lupus erythematosus inception cohort. J Rheumatol 2008;35:1776-81.
12. Hanly JG, Omisade A, Su L, Farewell V, Fisk JD. Assessment of cognitive function in systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis by computerized neuropsychological tests. Arthritis Rheum 2010;62:1478-86.
13. Wekking EM, Nossent JC, van Dam AP, Swaak AJ. Cognitive and emotional disturbances in systemic lupus erythematosus. Psychother Psychosom 1991;55:126-31.
14. Hay EM, Huddy A, Black D. A prospective study of psychiatric disorder and cognitive function in systemic lupus erythematosus. Ann Rheum Dis 1994;53:298-303.
15. Kozora E, Thompson LL, West SG, Kotzin BL. Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum 1996;39:2035-45.
16. Ginsburg KS, Wright EA, Larson MG, Fossel AH, Albert M, Schur PH, et al. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. Arthritis Rheum 1992;35:776-82.
17. Carbotte RM, Denburg SD, Denburg JA. Prevalence of cognitive impairment in systemic lupus erythematosus. J Nerv Ment Dis 1986;174:357-64.
18. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
19. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
20. Gladman DD, Ibañez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol 2002;29:288-91.
21. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.
22. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
23. Fries J, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.
24. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 2005;32:811-9.
25. Beck AT, Steer RA, Brown GK. Manual for Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
26. Ware Jr JE, Sherbourne CD. The MOS 36-item Short-form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
27. Dunn LM, Dunn L. Peabody Picture Vocabulary Test-Revised: Manual for forms L and M. Circle Pines, MN: American Guidance Service; 1981.
28. Snitz BE, Bieliauskas LA, Crossland AR, Basso MR, Roper B. PPVT-R as an estimate of premorbid intelligence in older adults. Clin Neuropsychol 2000;14:181-6.
29. Schmand B, Geerlings MI, Jonker C, Lindeboom J. Reading ability as an estimator of premorbid intelligence: Does it remain stable in emergent dementia? J Clin Exp Neuropsychol 1998;20:42-51.
30. Reeves D, Kane R, Winter K. Automated Neuropsychological Assessment Metrics (ANAM V3.11a/96) user's manual: clinical and neurotoxicology subset (Report No. NCRF-SR-96-01). San Diego: National Cognitive Foundation; 1996.
31. Reeves DL, Winter KP, Bleiberg J, Kane RL. ANAM genogram: historical perspectives, description, and current endeavors. Arch Clin Neuropsychol 2007;22 Suppl 1:15-37.
32. Bleiberg J, Garmoe WS, Halpern EL, Reeves DL, Nadler JD. Consistency of within-day and across-day performance after mild brain injury. Neuropsychiatry Neuropsychol Behav Neurol 1997;10:247-53.
33. Levinson DM, Reeves DL. Monitoring recovery from traumatic brain injury using Automated Neuropsychological Assessment Metrics (ANAM V1.0). Arch Clin Neuropsychol 1997;12:155-66.
34. Levinson D, Reeves D, Watson J, Harrison M. Automated Neuropsychological Assessment Metrics (ANAM) measures of cognitive effects of Alzheimer's disease. Arch Clin Neuropsychol 2005;20:403-8.
35. Wilken JA, Kane R, Sullivan CL, Wallin M, Usiskin JB, Quig ME, et al. The utility of computerized neuropsychological assessment of cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler 2003;9:119-27.
36. Townsend JT, Ashby FG. Stochastic modeling of elementary psychological processes. New York: Cambridge University Press; 1983.
37. Appenzeller S, Bertolo MB, Costallat LT. Cognitive impairment in rheumatoid arthritis. Methods Find Exp Clin Pharmacol 2004;26:339-43.
38. Hanly JG, Fisk JD, McCurdy G, Fougere L, Douglas JA. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol 2005; 32:1459-66.
39. Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt LA, et al. Are racial and ethnic minorities less willing to participate in health research? PLoS Med 2006;3:e19.
40. Sykes LL, Walker RL, Ngwakongnwi E, Quan H. A systematic literature review on response rates across racial and ethnic populations. Can J Public Health 2010;101:213-9.